Clinical Outcomes of Edoxaban Treatment in Atrial Fibrillation Patients with High Bleeding Risk: Insights from the ETNA-AF-China 1-Year Follow-up

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Background

- Atrial fibrillation (AF) patients with high bleeding risk often raise potential clinical concerns in China and many other countries.[1-2]
- Direct oral anticoagulants (DOACs) significantly reduce stroke/systemic embolic events (SEE) without increasing the risk of major, fatal bleeding for AF patients with bleeding risk factors.[3-4] However, the optimal dose of DOACs preventing stroke/SEE in these populations remains unclear.
- ETNA-AF-China (Edoxaban Treatment in routiNe clinical prActice in patients with nonvalvular Atrial Fibrillation-China) is a prospective, observational study conducted in 89 centres across the Chinese Mainland.
- Data from real-world studies including ETNA-AF-China, with regard to NOAC use in relation to clinical outcomes can clarify the concerns.

Purpose

To assess the effectiveness and safety of edoxaban treatment in Chinese AF patients with high bleeding risk, and to compare 60 mg vs 30 mg dose during 1-year follow-up of the ETNA-AF-China registry (NCT04747496)

Methods

- In this subgroup analysis, patients were evaluated by a DOAC score of bleeding risk factors[5]
  - DOAC score ≥6 (age, creatinine clearance, underweight, history of stroke/TIA/SEE, diabetes, hypertension, antiplatelet use, NSAIDs use, history of major/critical bleeding, liver disease) at baseline **[High bleeding risk]**
  - DOAC score <6 **[Moderate-to-low bleeding risk]**
- Patients were further categorized by different doses of edoxaban (60mg and 30 mg).
- The safety, effectiveness, and composite outcomes were reported by comparison between patient subgroups using Cox proportional hazards models.

Results

Patient baseline characteristics

- Of the 4883 patients with 1-year follow-up, 1534 (31.4%, 60 mg: n=518, 30 mg: n=1016) were identified as high bleeding risk, and 3349 (68.6%, 60mg: n=2126, 30 mg: n=1223) as moderate-to-low bleeding risk (**Figure 1**).
- Patients with high bleeding risk than moderate-to-low bleeding risk were primarily:
  - elderly (48.2% vs 1.3 % ≥80 years)
  - had lower body weight (5% vs 1.2% ≤45kg)
  - worse renal function (81% vs 44.1%)
  - higher CHA_2DS_2-VASc score (4.1 vs 2.3)
- In both the high-risk and moderate-to-low-risk subgroups, patients receiving 60 mg edoxaban were younger, with better renal function, and lower CHA_2DS_2-VASc scores than 30 mg (**Table 1**).

Figure 1. Patient distribution by bleeding risk stratification and dose group

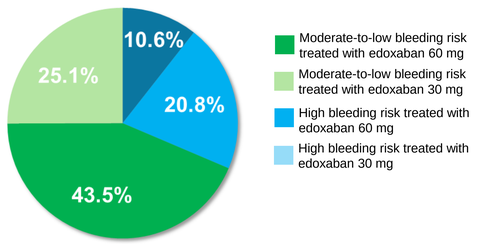


Table 1: Patient demographics and clinical history

	Moderate-to-low bleeding risk				High bleeding risk*				
	All (n = 3349)	Edoxaban 60 mg (n = 2126)	Edoxaban 30 mg (n = 1223)	*P-Value*[δ]	All (n = 1534)	Edoxaban 60 mg (n = 518)	Edoxaban 30 mg (n = 1016)	P-Value[†]	*P-Value*[ø]
Age, mean ± SD	66.3 ± 8.3	65.3 ± 8.2	68.1± 8.0	<0.001	78.9 ± 5.4	77.2 ± 5.2	79.8 ± 5.2	<0.001	<0.001
≥80 years	42 (1.3)	10 (0.5)	32 (2.6)	<0.001	740 (48.2)	173 (33.4)	567 (55.8)	<0.001	<0.001
Male	2044 (61.0)	1490 (70.1)	554 (45.3)	<0.001	738 (48.1)	319 (61.6)	419 (41.2)	<0.001	<0.001
Weight [kg], mean ± SD	69.9 ± 12.4	74.0 ± 11.2	62.8 ± 11.3	<0.001	63.5 ± 11.5	70.1 ± 9.7	60.1 ± 10.8	<0.001	<0.001
≤45 kg	41 (1.2)	1 (0.0)	40 (3.3)	<0.001	77 (5.0)	2 (0.4)	75 (7.4)	<0.001	<0.001
Creatinine clearance [mL/min], mean ± SD	80.2 ± 26.1	86.2 ± 25.7	69.9 ± 23.4	<0.001	52.8 ± 19	63.5 ± 19.6	47.7 ± 16.3	<0.001	<0.001
15–30 mL/min	10 (0.3)	1 (0.0)	9 (0.7)	<0.001	117 (7.6)	8 (1.5)	109 (10.7)	<0.001	<0.001
Hypertension	2232 (66.6)	1520 (71.5)	712 (58.2)	<0.001	1351 (88.1)	480 (92.7)	871 (85.7)	<0.001	<0.001
Diabetes mellitus	716 (21.4)	511 (24)	205 (16.8)	<0.001	568 (37.0)	229 (44.2)	339 (33.4)	<0.001	<0.001
Dyslipidemia	822 (24.5)	570 (26.8)	252 (20.6)	<0.001	402 (26.2)	154 (29.7)	248 (24.4)	0.029	0.227
Heart failure	468 (14.0)	267 (12.6)	201 (16.4)	0.002	246 (16.0)	55 (10.6)	191 (18.8)	<0.001	0.064
COPD	135 (4.0%)	82 (3.9%)	53 (4.3%)	0.559	98 (6.4)	27 (5.2)	71 (7.0)	0.217	<0.001
Coronary heart disease	1272 (38.0)	799 (37.6)	473 (38.7)	0.555	852 (55.5)	287 (55.4)	565 (55.6)	0.982	<0.001
Renal impairment	1477 (44.1)	767 (36.1)	710 (58.1)	<0.001	1242 (81.0)	368 (71.0)	874 (86.0)	<0.001	<0.001
History of ischaemic stroke	179 (5.3)	111 (5.2)	68 (5.6)	0.734	172 (11.2)	59 (11.4)	113 (11.1)	0.943	<0.001
History of major bleeding	10 (0.3)	9 (0.4)	1 (0.1)	0.104	40 (2.6)	20 (3.9)	20 (2.0)	0.042	<0.001
Longterm use of NSAIDs	33 (1.0)	20 (0.9)	13 (1.1)	0.870	51 (3.3)	34 (6.6)	17 (1.7)	<0.001	<0.001
Current use of antiplatelets	88 (2.6)	58 (2.7)	30 (2.5)	0.714	211 (13.8)	85 (16.4)	126 (12.4)	0.038	<0.001
CHA_2DS_2-VASc, mean ± SD	2.3 ± 1.1	2.2 ± 1.1	2.5 ± 1.1	<0.001	4.1 ± 1.2	4.0 ± 1.1	4.2 ± 1.2	0.002	<0.001
Mod. HAS-BLED, mean ± SD	1.4 ± 0.9	1.3 ± 0.9	1.6 ± 0.9	<0.001	2.5 ± 0.8	2.4 ± 0.9	2.5 ± 0.8	0.386	<0.001

*DOAC score ≥6 point. [δ]*P*-value between moderate-to-low bleeding risk and high bleeding risk. [ø]*P*-value between 60 mg and 30 mg edoxaban for treating patients with high bleeding risk, and [†]*P*-value for treating patients with moderate-to-low bleeding risk. DOAC score: age, creatinine clearance, underweight (body mass index <18.5 kg/m^2), stroke/transient ischemic attack/embolism history, diabetes, hypertension, antiplatelet use, aspirin, dual-antiplatelet, nonsteroidal anti-inflammatory (NSAID) use, bleeding history, liver disease (bilirubin>2xULN = Yes and AST/ALT >3xULN).

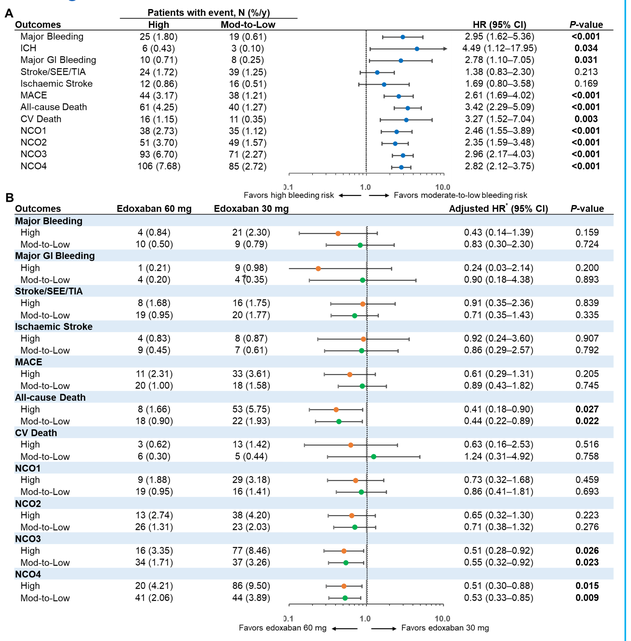
Clinical outcomes by bleeding risk stratification

- Annualized event rates of major bleeding (HR: 2.95, 95% CI: 1.62–5.36; *P*<0.001), all-cause death (3.42, 2.29–5.09; *P*<0.001), CV death (3.27, 1.52–7.04; *P*=0.003), major adverse cardiac events (MACE, 2.61, 1.69–4.02; *P*<0.001) and all net clinical outcomes (NCOs) were significantly higher in patients with high bleeding risk compared with moderate-to-low risk (**Figure 2A**).

Dose-outcome association

- When compared to an edoxaban dose of 30mg, 60 mg was associated with significantly lower rates of all-cause death (adjusted HR: 0.41, 0.18–0.90; *P*=0.027), a lower trend of NCO3 (0.51, 0.28–0.92; *P*=0.026) and NCO4 (0.51, 0.30–0.88; *P*=0.015) by a composite of stroke/SEE, major bleeding and death events in the high-risk subgroup (**Figure 2B**).
- No significant differences between edoxaban doses and stroke or bleeding outcomes with cumulative low event rates were observed.

Figure 2. Outcome events (A) stratified by bleeding risk, and (B) association with edoxaban doses among high, moderate-to-low bleeding risk status



*Adjustment for age, CrCl, weight, history of stroke/TIA/SEE, antiplatelet use. NCO1 = ischaemice stroke/SEE or major bleeding; NCO2 = ischaemice stroke/SEE, TIA, MI, venous thrombosis (DVT/PE), or major bleeding; NCO3 = ischaemice stroke/SEE, major bleeding, or all-cause death; NCO4 = ischaemice stroke /SE, TIA, MI, venous thrombosis, major bleeding, or all-cause death, CV death. High, patients with high bleeding risk; Mod-to-Low, patients with moderate-to-low bleeding risk.

Conclusions

- **In routine clinical care, AF patients at high bleeding risk face worse outcomes of death events, MACE, as well as the composite outcomes over moderate-to-low-risk patients.**
- **Among patients with high bleeding risk, edoxaban use showed effectiveness and safety with overall low incidence and potential better survival; composite endpoint benefit could be associated with 60mg.**
- **Further investigation is ongoing.**

Conflict of interest

C.-S.M. has received honoraria from BristolMyers Squibb, Pfizer, Johnson & Johnson, Boehringer-Ingelheim, Bayer and Daiichi Sankyo for giving lectures. No fees are directly received personally. J.D., Y.Y. and J.X. are employees of Daiichi Sankyo (China) Holdings Co., Ltd, Shanghai, China. M.U. and C.C. are employees of Daiichi Sankyo Inc. Basking Ridge, New Jersey, USA. All remaining authors have no disclosures.

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